Diagnosis and Management of Endomyocardial Fibrosis

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KEYWORDS

• Endomyocarial fibrosis • Restrictive cardiomyopathy • Heart failure • Neglected diseases

KEY POINTS

- Endomyocardial fibrosis is an important cause of restrictive cardiomyopathy worldwide.
- The etiology of endomyocardial fibrosis remains elusive, and the disease is most often diagnosed in the late stages of disease.
- Medical management is of little benefit, and although surgical intervention offers some survival advantage, access is limited in low-resource settings.
- International collaboration, modern research techniques, and increased funding are needed to improve understanding of this neglected tropical disease.

INTRODUCTION

Endomyocardial fibrosis (EMF), one of the world's most neglected cardiovascular diseases, remains an important cause of restrictive cardiomyopathy. Worldwide prevalence is estimated at 10 to 12 million,[1] although systematic global epidemiology is extremely limited. Most cases occur in tropical, low-resource settings, and poverty is a multifactorial driver of disease development, contributes to late diagnosis, and limits access to appropriate medical and surgical care. Knowledge advancement around EMF has been slow, and significant questions remain on the etiology, natural history, and best therapeutic strategies. Increased awareness, advocacy, and research are needed to further understand this neglected tropical cardiomyopathy and to improve survival of those affected.

EPIDEMIOLOGY

EMF remains primarily a tropical cardiomyopathy with most cases coming from Africa, Asia, and South America. African cases have clustered in Uganda, Nigeria, the Ivory Coast, and the coastal areas of Mozambique, but 16 countries distributed across the continent have reported cases.[2] Outside of Africa, hotspots include Kerala State in India,[3–5] Guangzi providence in China,[6] and Brazil.[7]

Geographic restriction and regional variation within high prevalence countries has been noted. In Mozambique, almost two-thirds of patients presenting at a tertiary center with EMF resided in a single costal province.[8] Ethnic predisposition is reported, with EMF being more common among Rwandan and Burundian immigrants living in Uganda compared with native Ugandans,[9,10] although Rwanda and Burundi report few primary cases.

Conflicts of Interest: The authors have nothing to disclose.

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Accurate estimates of the incidence and prevalence of EMF remain challenging. A single population screening, conducted in an endemic area of Mozambique, suggests EMF may have a much broader disease spectrum and much higher prevalence than previously thought. Echocardiographic screening of 948 residents of the Inharrime district found 19.8% with evidence of EMF, 77.3% of whom had mild disease.[11] Case detection was higher among family members, and risk increased with each additional positive case within a family, a finding previously reported in Uganda[12] and Zambia.[13]

EMF patients most typically come from the lowest socioeconomic groups, even within broadly low-income countries.[9,14] Classically, EMF presents in childhood and adolescence, although some sites report a bimodal distribution with second peak among women in childbearing years.[9,15] Extreme presentations in infancy[16,17] and the elderly[11] have also been reported. Several studies found no sex specific preponderance, whereas others show conflicting higher rates among women (Uganda[15]) and among men (Mozambique,[11] Nigeria[18]).

Evidence shows that incidence and prevalence of EMF may be decreasing in some regions, potentially because of improving socioeconomic conditions.[19] In the last half-century, parts of Nigeria have seen a decrease from 10% to less than 1% prevalence.[20] Similarly, high-incidence regions of India have reported dramatic declines.[19] In contrast, cases of EMF are being reported from countries that historically have not been affected (Malawi[21]), likely secondary to increasing availability of echocardiography.[2] Other regions, such as Uganda,[22] report no change, and in most affected countries, no trend data have been collected.

ETIOLOGY

There is no clear consensus on the etiology of EMF. Authentication and replication of individual hypotheses has been difficult. Poor recognition and characterization of the early disease state and the relative scarcity of contemporary investigations using modern techniques have further compounded this challenge. Poverty and geographic specificity have emerged as the most consistent risk factors and are intimately related to most proposed etiologies, which are grouped into the 3 main categories of eosinophilia and parasitic disease, diet and toxicity, and genetic susceptibility.[23]

EMF is most prevalent in tropical regions, which are also plagued by infectious and parasitic disease. Specific trigger pathogens have been proposed including malaria,[24,25] streptococcus,[26,27] fillariasis,[28–30] and schistosomiasis,[27,31] among others. However, imperfect matching of pathogens with EMF distribution[32,33] and inconsistent parasitic loads in affected patients[34] argue against direct infection as a single infectious trigger. A common immune overreaction, resulting from a variety of different pathogens, is more plausible. Associations with increased circulating IgE[28,35] and eosinophilia[31,36] have been reported, and specific hyperimmune conditions, such as malarial hypersplenomegaly syndrome have been linked to EMF development.[12] Here again, however, there are inconsistencies, suggesting that at most, the immune response is one of several components of EMF development.

Dietary deficiencies (magnesium[37]) and excesses (vitamin D[38]), ingested toxins (cerium, cyanogenic glycosides,[39] serotonin[40,41]), and herbal preparations[39] have also been proposed as causative. The right-sided predilection for EMF supports the potential role of a toxin, filtered from the blood in the pulmonary circulation.[19] Cassava, a root vegetable nearly ubiquitous to the diet of certain low-income countries, has been studied most extensively, with some evidence of endocardial thickening and fibrosis in mice fed a cassava-rich diet.[42] However, as happens with parasitic load,[43] cassava consumption is typically proportionate to poverty level.[19]

It is most likely that EMF results from the complex interplay of a susceptible host being exposed to environmental challenges through the conditions of extreme poverty (including infectious and dietary challenges). Familial clustering of EMF cases has been reported from Uganda,[12] Nigeria,[44] Zambia,[13] and Mozambique.[11] A single formal genetic analysis conducted in 2 populations found polymorphisms in the human leukocyte antigen system to be associated with a predisposition to EMF.[45] Further formal genetic studies, ideally unbiased genomewide investigations, are of critical importance and may find new insights into the pathogenesis of EMF.

NATURAL HISTORY

EMF patients typically present late, when serious cardiovascular symptoms and complications develop. Thus, although the late stages of EMF have been extensively reported, it has been more challenging to characterize the patterns and presentations of early disease. The current understanding of EMF involves progression through 3 disease stages: an active inflammatory stage, a